

830010-2002.2
09/975,812**REMARKS**

Claims 11, 17-20, 23-26 and 36 and 37 are pending in the instant application. Claim 11 has been amended to clarify the subject matter of the present invention and to round out the scope of protection to which Applicants are entitled; i.e., the claim amendment was not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103, or 112. Reconsideration and withdrawal of all rejections of the application, and allowance of the claims, especially in view of the amendments and remarks made herein and the documents herewith, are respectfully requested.

Support for the amendments to the specification can be found in the text of the instant application. Table 2 has been amended to correct an obvious typographical error in the ED₅₀ (mM) of lidocaine alone. Support for this correction can be found on page 26, in Table 1, where the ED₅₀ (mM) of lidocaine alone is stated to be 2.5 mM. The value for the ED₅₀ (mM) of lidocaine alone is also depicted in Figure 3b (X-axis) as 2.5 mM. No new matter is added. *See Application of Oda*, 443 F.2d 1200, 170 U.S.P.Q. 268 (C.C.P.A. 1971).

Support for amending the specification to state that the fixed ratio of lidocaine/buprenorphine is 2.5 mM can be found in Table 1, wherein the correct ratio of 2.4 is evident from the ED₅₀ values listed for lidocaine and buprenorphine (i.e., 0.44/0.18 = 2.4). No new matter is added. *Id.*

Claim 11 has been amended to recite a morphine to lidocaine ratio of about 1:0.1 to about 1:2.4. Support for this range of ratios can be found within the Examples section of the specification. In Example 1, a morphine to lidocaine ratio of about 1:0.6 was administered (i.e., 1.5 mM morphine/0.9 mM lidocaine), and synergism was described (Figure 3a). In Example 3, a morphine to lidocaine ratio of about 1:0.5 was administered (i.e., 0.25 mg/ml morphine/0.125 mg/ml lidocaine), and synergism was also described.

The morphine to lidocaine ratios administered to subjects in Example 2 is also between about 1:0.1 to about 1:2.4. The results are presented in Table 2, and Figure 3b. The table below summarizes the morphine to lidocaine ratio in the individual dosage forms administered, as described in the accompanying declaration under 37 C.F.R. § 1.132 of Dr. Gavril Pasternak;

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Morphine Dosage	Lidocaine Dosage	Morphine to Lidocaine Ratio ¹
1.5 mM morphine	0.22 mM lidocaine	1:0.2
1.5 mM morphine	0.45 mM lidocaine	1:0.3
1.5 mM morphine	0.9 mM lidocaine	1:0.6
1.5 mM morphine	1.8 mM lidocaine	1:1.2
3.0 mM morphine	0.45 mM lidocaine	1:0.2
3.0 mM morphine	0.9 mM lidocaine	1:0.3
3.0 mM morphine	1.8 mM lidocaine	1:0.6
4.5 mM morphine	0.22 mM lidocaine	1:0.1
4.5 mM morphine	0.45 mM lidocaine	1:0.1
4.5 mM morphine	0.9 mM lidocaine	1:0.2
0.4 mM morphine	0.45 mM lidocaine	1:1.3
0.75 mM morphine	0.45 mM lidocaine	1:0.6
1.5 mM morphine	0.45 mM lidocaine	1:0.3
3.0 mM morphine	0.45 mM lidocaine	1:0.2
6.0 mM morphine	0.45 mM lidocaine	1:0.1
0.75 mM morphine	0.9 mM lidocaine	1:1.2
1.5 mM morphine	0.9 mM lidocaine	1:0.6
3.0 mM morphine	0.9 mM lidocaine	1:0.3
4.5 mM morphine	0.9 mM lidocaine	1:0.2
0.75 mM morphine	1.8 mM lidocaine	1:2.4
1.5 mM morphine	1.8 mM lidocaine	1:1.2
3.0 mM morphine	1.8 mM lidocaine	1:0.6
4.5 mM morphine	1.8 mM lidocaine	1:0.4

New claim 37 has been added to recite an ED₅₀ morphine to lidocaine ratio of about 1:0.2 to about 1:3.5. Support for this range of ratios can be found within the Examples section of the specification. The ED₅₀ morphine to lidocaine ratio administered to subjects in Example 2, as shown in Table 2, is between about 1:0.2 to about 1:3.6. The table below summarizes the morphine to lidocaine ratios administered:

¹ Ratios are rounded to the nearest tenth.

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Morphine ED ₅₀	Lidocaine ED ₅₀	Morphine to Lidocaine Ratio ²
1.0 mM morphine	2.5 mM lidocaine	1:2.5
0.8 mM morphine	2.5 mM lidocaine	1:3.1
0.7 mM morphine	2.5 mM lidocaine	1:3.6
6.1 mM morphine	3.6 mM lidocaine	1:0.6
6.1 mM morphine	1.5 mM lidocaine	1:0.3
6.1 mM morphine	1.3 mM lidocaine	1:0.2

By comparison, Saito et al. ("Saito") required a morphine to lidocaine ratio of 1:666 (i.e., 0.3 ug/kg/h morphine and 200 ug/kg/h lidocaine), administered directly into the central nervous system, to produce a synergistic effect.³ Saito provides no suggestion or motivation for a topical composition of morphine and lidocaine, much less one within the claimed ranges.

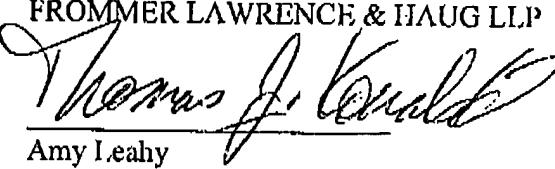
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPI are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

In view of the declaration and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,
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² Ratios are rounded to the nearest tenth.

³ The following concentrations (in percent w/v) were used: 0.12% morphine (0.3 µg/kg/h in 250 µl volume) and 80% lidocaine (200 µg/kg/h in 250 µl volume).